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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

10890-2 MIS:jb

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

09/ 674172

INTERNATIONAL APPLICATION NO.

PCT/EP99/02930

INTERNATIONAL FILING DATE

April 29, 1999

PRIORITY DATE CLAIMED

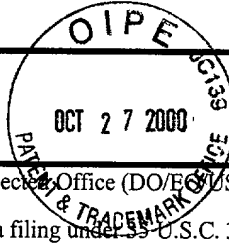
April 29, 1998

TITLE OF INVENTION

TREATMENT OF PAPILLOMA VIRUS INFECTION USING A MYCOBACTERIUM

APPLICANT(S) FOR DO/EO/US

Andreas BÖHLE; and Dieter JOCHAM



Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). - unsigned copy
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/674172

INTERNATIONAL APPLICATION NO.

PCT/EP99/02930

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21. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☒ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =**CALCULATIONS PTO USE ONLY**

\$1,000.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	25 - 20 =	5	x \$18.00
Independent claims	3 - 3 =	0	x \$80.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>
TOTAL OF ABOVE CALCULATIONS			=
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).			<input type="checkbox"/>
SUBTOTAL			=
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+
TOTAL NATIONAL FEE			=
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).			<input type="checkbox"/>
TOTAL FEES ENCLOSED			=
			Amount to be:
			refunded
			charged

\$90.00

\$0.00

\$0.00

\$1,090.00

\$0.00

SUBTOTAL

\$1,090.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00

TOTAL NATIONAL FEE

\$1,090.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

\$0.00

TOTAL FEES ENCLOSED

\$1,090.00

Amount to be:
refunded
charged

\$
\$

☒ A check in the amount of \$1,090.00 to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 19-2253 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Michael I. Stewart
Sim & McBurney
6th Floor, 330 University Avenue
Toronto, Ontario
Canada, M5G 1R7.



24223

PATENT TRADEMARK OFFICE

Michael I. Stewart
SIGNATURE

Michael I. Stewart

NAME

24,973

REGISTRATION NUMBER

October 26, 2000

DATE

09/ 674172

526 Rec'd PCT/PTO 27 OCT 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Our Ref: 10890-2 MIS:jb

In re National Phase of International Application

No.: PCT/EP99/02930

International
Filing Date: April 29, 2000

Applicant: Andreas Böhle; and Dieter Jocham

Title: TREATMENT OF PAPILLOMA VIRUS INFECTION
USING A MYCOBACTERIUM

PRELIMINARY AMENDMENT

The Commissioner of Patents
and Trademarks,
Washington, D.C. 20231,
U. S. A.

Dear Sir:

Please amend this application in the following manner:

In the Disclosure:

Before the first line of the specification, add the following:

" REFERENCE TO RELATED APPLICATIONS

This application is a national phase application under 35 U.S.C. 371 of
PCT/EP99/02930."

REMARKS

The specification has been amended on page 1 to reflect that this
application is a U.S. National Phase filing under 35 U.S.C. 371 of PCT/EP99/02930.

Respectfully submitted,

Michael I. Stewart
Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada
(416) 595-1155
FAX No. (416) 595-1163

Date: October 26, 2000

PTO/PCT Rec'd-27 OCT 2000TITLE OF THE INVENTIONTREATMENT OF PAPILLOMA VIRUS INFECTION USING A MYCOBACTERIUM

5

FIELD OF INVENTION

The present invention relates to the treatment of disease caused by papilloma virus infection in humans, in particular to the treatment of condylomata acuminata caused by human papilloma virus in humans.

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BACKGROUND OF THE INVENTION

Human papilloma virus (HPV) infections of the urogenital tract represent the most often sexually transmitted viral disease in humans (refs. 1 to 3 - various references are referred to in parenthesis to more fully describe the state of the art to which this invention pertains. Full bibliographic information for each citation is found at the end of the specification, immediately preceding the claims. The disclosure of these references are hereby incorporated by reference into the present disclosure). HPV is a double stranded DNA virus and with the recent developed molecular biological techniques, more than 55 different HPV types have been recognized (ref. 4). HPV is associated with a wide spectrum of clinical states including condylomata acuminata, latent and subclinical infection, and Bowen's disease. Subclinical infections gain more importance as they are believed to cause intraepithelial neoplasia, based on the frequent detection of HPV DNA in invasive carcinomas, especially in urogenital region (refs. 1, 5). A significant risk for the development of an invasive cancer is ascribed to the infections by HPV types 16, 18 and 33 (refs. 6 to 9).

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The most prevalent HPV types causing condylomata acuminata are type 6 and 11. Condylomata acuminata are visible, multifocal, multicentric and

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multiform lesions. Predilection sites are penis, scrotum, perineum, urethra, perianal regions, intertriginous zones, and oral mucosa. In uncircumcised men the frenulum, the coronary sulcus and the inner aspect of the foreskin are most often afflicted, whereas in circumcised patients the shaft of the penis is involved. Genital warts are of great psychological and cosmetic relevance representing a major hindrance to sexual performance.

Treatment options include surgical methods like excision, electrocautery, cryosurgery or laser vaporization. It has been shown in molecular hybridization studies that HPV DNA sequences exist in adjacent normal tissue after carbon dioxide laser removal of genital warts (ref. 10). These findings and the well known high recurrence rates after initial treatment demonstrate the need for adjuvant therapy to eradicate invisible disease. Therapeutic results with local application of cytotoxic agents, for example, 5-fluorouracil and podophyllin/podophyllotoxin have, however, been unsatisfactory (refs. 11 to 13). Furthermore, several types of interferons (IFN) as well as autologous vaccines have been tried with varying success (refs. 2, 14 to 17). More recently, oral isotretinoin has been given with some success to reduce the recurrence rate (refs. 18, 19, 20).

SUMMARY OF INVENTION

In accordance with one aspect of the present invention, there is provided a method of treatment of disease caused by papilloma virus, which comprises applying an effective amount of *Mycobacterium* to the region of infection.

In particular, the present invention in accordance with the treatment of infections caused by human papilloma virus (HPV) using the *Mycobacterium*. Such infection may include cutaneous and genital warts in humans, including verruca vulgaris and condyloma acuminatum, cervical intraepithelial neoplasia and genital carcinomas. In general, the treatment is

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applicable to any disease condition caused by HPV in humans including penile, intraurethral, perianal, intra-anal or perineal infections in men and cervical, vaginal, perigenital, intra-urethral, intra-anal and perineal infections in women, including condylomata acuminata, penile cancer, Bowen's disease, cervical cancer, head and neck cancer, laryngeal papillomatosis and laryngeal carcinoma. The present invention is illustrated by application to recurrent external and intraurethral condylomata acuminata in men.

The *Mycobacterium* which may be employed may be an attenuated form of a *Mycobacterium* of the tuberculosis complex and, in particular, may be an attenuated form of *M. bovis*, specifically Bacillus Calmette-Guerin (BCG).

The treatment may be effected by application of the *Mycobacterium* in a suitable carrier to the region of infection, which may involve topical application to cutaneous, penile and perianal areas, or intraurethral application to the urogenital tract. The treatment also may be effected by inhalation, oral application or as an enema. The treatment may involve a single or a plurality of doses applied at time intervals. The individual dosage level may be about 1 mg to about 500 mg while the time interval between doses may vary from about 1 to about 30 days. The number of treatments applied is from 1 to about 30 treatments. The treatment may be preceded by laser or other surgical or topical therapy.

The *Mycobacterium* may be formulated with a keratolytic agent for topical application to the region of infection, particularly as a cream for adherent application to the region of infection. The keratolytic agent may be salicylic acid, which may be powdered. The keratolytic agent may be present in an amount of about 0.1 to about 50 wt%, preferably about 1 to about 10 wt%.

The composition which is applied to the area of infection may take any desired form, for example, a cream, a powder or ointment. Any desired

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form of application may be employed, including slow-release systems, plasters and transdermal systems.

The present invention further includes, in an additional aspect thereof, a therapeutic composition for the treatment of a disease condition caused by papilloma virus, comprising an effective amount of a *Mycobacterium* formulated with a keratolytic agent for topical application to a region of infection. Such composition may be formulated as described above.

The present invention extends, in a further aspect thereof, to the use of a *Mycobacterium* in the manufacture of a medicament for the treatment of infection caused by papilloma virus, particularly human papilloma virus.

GENERAL DESCRIPTION OF INVENTION

A wide spectrum of therapeutic approaches has been used over the past years for the management of condylomata acuminata. However, no form of therapy has yielded consistently effective results. In order to avoid recurrence of disease, the combination of surgical ablative methods and immunomodulative agents seem to be promising. Due to their antiviral, immunomodulative and antiproliferative properties, interferons have been given as a topical and systemic form of treatment for condylomata acuminata. Interferons were also chosen for their mild side effect profile but recurrence rates up to 75% have been reported (refs. 2, 14 to 17).

In the case studies reported below, patients treated with BCG were cleared of warts and cytological evidence of HPV and had no recurrence of disease. One set of patients had previously experienced between two and five recurrences of condylomata acuminata. The annual recurrence rate was significantly reduced from 3.2 with standard therapy to 0.75 with BCG therapy. The incidence of side effects due to BCG therapy was low. One patient reported mild dysuria after the second and third BCG application of

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this first treatment course. Another patient had a penile edema and fever which was managed conservatively. Penile edema is a rare complication after intravesical BCG instillation. However, with intraurethral instillation of BCG for transitional cell carcinoma of the urethra has been reported by Baniel et al (ref. 21). Serious complications like sepsis or hematuria were not observed in the reported group.

A second set of patients had no previous treatment for the condition and were given treatment with BCG without prior laser surgery. Complete disappearance of all visible condylomata acuminata was achieved in six out of eight patients and no relapse was reported. Incomplete regression was obtained in two cases. No side effects were reported.

EXAMPLES

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Example. These Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

Example 1

This Example contains the results of clinical trials in which BCG was used as adjuvant therapy to laser surgery.

Between October 1994 and March 1997, six men with rapidly recurrent external and intraurethral condylomata acuminata were selected for BCG therapy. The mean age was 27 years (range 22 to 32 years). All patients had previously undergone therapy for recurrent condylomata acuminata in

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other dermatological and urologic departments (see Table 1 below). The patients were informed they were undergoing an experimental treatment approach and all individuals gave written informed consent.

5 Examination of the penis and scrotum was performed without and with acetic acid application and lesions were treated with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Dornier Medilas Fibertome 4060) at 10 to 20 W. Endoscopic inspection of the urethra and bladder was also performed and visible lesions treated with the Nd:YAG
10 laser. Finally, the perianal region was inspected and laser treatment, when necessary, applied.

A minimum interval of 3 weeks between laser therapy and BCG application was utilized. For internal application of BCG, 81 mg of Connaught strain
15 (Pasteur Mérieux Connaught Canada, North York, Ontario, Canada) were dissolved in 2 ml. of sterile saline. The solution was directly instilled into the urethra with low pressure and kept for a minimum of 2 hours. To avoid preliminary emptying, a dressing was taped over the meatus. After 2 hours, the dressing was removed and the patient allowed to void
20 spontaneously. A total of six BCG instillations were given at weekly intervals.

For external application, eighty-one mg of BCG Connaught strain were again dissolved in 2 ml of sterile saline. The solution was put onto a dressing
25 which was gently wrapped around the sulcus and other affected areas. The dressing was fixed and kept for 2 hours as a moist chamber. This procedure was also repeated six times at weekly intervals.

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The courses of six patients are given below and in Table 1 below:

Case 1

5 A 22-year-old male patient developed condylomata acuminata in 1994. Initially, the frenulum and the meatus were involved. He was treated with local podophyllin but relapsed twice, and was referred to the urological department in April 1995. Over a period of 13 months, five relapses occurred despite internal and external laser application. From July until
10 October 1996, six intraurethral instillations and external applications of BCG were given in weekly intervals. At follow-up of 11 months, no relapse had been noticed.

Case 2

15 A 28-year-old male patient demonstrated with perianal and preputial condylomata in May 1995. Cystoscopy revealed additional lesions of the urethra and, therefore, internal and external laser therapy was performed. Three months later an urethral relapse was diagnosed and again treated
20 with laser. Subsequently, the patient received six intraurethral instillations combined with external application of BCG. At follow-up of 29 months, no relapse had been noticed.

Case 3

25 A 26-year-old male patient had initial diagnosis of condylomata acuminata in 1992. The affected sites included the meatus and frenulum as well as the perianal region. Over a period of 15 months, four relapses occurred which were all managed with laser therapy. In September 1995,
30 intraurethral instillation and external application of BCG was performed. At follow-up of 24 months, no relapse had been noticed.

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Case 4

A 32-year-old man developed condylomata acuminata in February 1995. He had a hypospadias without operative correction required. Initial involvement included the meatus, subsequently frenulum and urethra had been involved. During the next 16 months, four relapses were diagnosed and treated with laser. Intraurethral BCG was given in August and September 1996. After 2 further relapses, intraurethral instillation and external application of BCG was repeated in January and February 1997. At follow-up of 8 months, no relapse had been noticed.

Case 5

A 31-year-old male had initial diagnosis of condylomata acuminata in January 1993. Primarily, meatus and foreskin were affected. In the next 27 months, four relapses occurred and managed with laser therapy. The first course of intraurethral instillation and external BCG application was performed in May and June 1995. The patient had three relapses which were treated with laser. In June and July 1996, he received a second course of BCG. He demonstrated one relapse which was lasercoagulated and at follow-up of 12 months, no further relapse had occurred.

Case 6

A 27-year-old male patient demonstrated condylomata acuminata in August 1996. Penis, meatus and urethra were involved. After two relapses, BCG was applied in July 1997. Due to side effects, the treatment was stopped after the third instillation. He had demonstrated a penile edema and fever (38.5°C) and was treated with antiphlogistic drugs and ice packages. At follow-up of 3 months, one new penile lesion had developed.

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In summary of the clinical results obtained in this Example, three patients completed one course of BCG. These patients had no relapse in follow-up studies (Table 1). Two patients underwent a second course of BCG after recurrence of condylomata acuminata. One of them remained without relapse after the second course in a follow-up period of 8 months. The other patient had one relapse after the second BCG course. One patient developed a relapse after he had discontinued therapy due to side effects following the third BCG instillation of his first course.

With respect to side effects, one patient reported mild dysuria after the second and third BCG instillation of his first treatment course. Another patient was withdrawn from BCG therapy due to penile edema and fever. No other side effects were reported.

Before BCG therapy, 36 recurrences of condylomata acuminata were noted in 136 observation months compared to 6 episodes during 96 months after treatment. Therefore, the annual recurrence rate before BCG therapy was 3.2 and 0.75 thereafter. These results were statistically significant ($p < 0.05$, test of equality of 2 percentages, (ref. 22).

Example 2

This Example contains the results of clinical trials in which BCG was used alone without prior laser surgery.

A group of eight men with primary external ($n = 6$) and intraurethral ($n = 2$) condylomata acuminata, who had no previous treatment for the condition, were treated by six applications or instillations of BCG, given at weekly intervals, following the protocol described in Example 1, but without any prior laser surgery.

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The preparation employed was prepared as follows:

30 mg of salicylic acid powder plus 30 mg of an inert vehicle consisting of
0.5% silicon dioxide in D-mannitol was dissolved and suspended in 3 ml
sterile (0.9%) saline.

81 mg of Connaught strain BCG then was added to form a paste or cream.
The paste or cream adhered very well to the skin. After application or
instillation a condom was applied for two hours and no further dressing
applied.

In six of the eight cases, there was a disappearance of all visible
condylomata acuminata, as determined both by external inspection and by
the acetic acid test. No patient has yet reported a relapse.

In the other two cases, both with meatal condylomata, there was only
incomplete regression and both patients received a second course of BCG
treatment following Nd:YAG laser treatment.

No side effects were reported by any of the patients.

SUMMARY OF DISCLOSURE

In summary of this disclosure, BCG therapy is useful in treating
condylomata acuminata, particularly rapidly recurrent conditions. In
general, *Mycobacteria* are useful in treating infections caused by papilloma
virus. Modifications are possible within the scope of this invention.

TABLE 1

Patient #	AG E	No. previous occurrences	No. relapses before BCG	No. relapses after BCG	Localisation of relapses before BCG	Localisation of relapses after BCG
1	22	3	5	0	Urethra, frenulum, meatus	
2	28	1	2	0	foreskin, perianal	
3	26	5	4	0	frenulum, urethra, meatus	
4	32	1	4	2,0 after 2 nd course	frenulum, urethra, urethra	frenulum, urethra
5	27	3	4	3,0 after 2 nd course	foreskin, meatus urethra	foreskin, meatus urethra
6	27	1	3	1 (incomplete course)	meatus, urethra	meatus, urethra

REFERENCES

1. Syrjänen K.J.: HPV in genital squamous cell tumors: epidemiology and clinical synopsis. In, Genital Papillomavirus Infections. Edited by G. Gross, S. Jablonska, H. Pfister and H. E. Stegner. Berlin Heidelberg New York: Springer-Verlag, pp. 3-12, 1990.
2. Bonnez W., Oakes, D., Bailey-Farchione, A., Choi, A., Hallahan, D., Pappas, P., Holloway, M., Corey, L., Barnum, G., Dunne, A., Stoler, M.H., Demeter, L.M. and Reichman, R.C.: A randomized, double-blind, placebo-controlled trial of systemically administered interferon- α , - β , or - γ in combination with cryotherapy for the treatment of condyloma acuminatum. J. Infect. Dis., 171:1081, 1995
3. Grin, W.: Condyloma acuminata-Epidemiologie und Therapie. Wien. Kin. Wochenschr., 104:215,1992.
4. Barrasso, R., de Brux, J., Croissant, O. and Orth, G.: High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N. Engl. J. Med., 317: 916,1987.
5. von Knebel Doeberitz, M. and zur Hausen, H.: Biological significance of human papillomavirus early gene expression in human cervical carcinoma cells. In: Genital Papillomavirus Infections. Edited by G., Gross, S. Jablonska, H. Pfister and H.E. Stegner. Berlin Heidelberg New York: Springer-Verlag, pp.51-65, 1990.

6. Smith, K.T. and Campo, M.S.: Papillomaviruses and their involvement in oncogenesis. Biomed. Pharmacoth., 39: 405, 1985.
- 5 7. Pfister, H.: Biology and Biochemistry of Papillomaviruses. Rev. Physiol. Biochem. Pharmacol., 99: 111, 1984.
8. Syrjänen, S.M., von Krogh, G. and Syrjänen, K.J.: Detection of human papillomavirus DNA in anogenital condylomata in men using in situ DNA hybridisation applied to paraffin sections.
10 Genitourin. Med., 63: 31. 1987.
9. Wiener, J.S., Effert, P.J., Humpphrey, P.A, Yu, L., Liu, E.T. and Walter, P.J.: Prevalence of human papilloma virus types 16 and
15 18 in squamous-cell carcinoma of the penis: a retrospective analysis of primary and metastatic sections by differential polymerase chain reaction. Int. J. Cancer, 50:694, 1992.
10. Ferenczy, A., Mitao, M., Nagai, N., Silverstein, S.J. and Crum, C.P.: Latent papillomavirus and recurrent genital warts. N. Engl. J. Med., 313: 784, 1986.
20
11. Swinehart, J.M., Sperling, M., Phillips, S., Kraus, S., Gordon, S., McCarty J.M., Webster G.F., Skinner, R., Korey, A. and Orenberg, E.K: Intralesional fluorouracil/epinephrine injectable gel for
25 treatment of condylometa acuminata. A phase 3 clinical study. Arch. Dermatol., 133: 67, 1997.
12. von Krogh, G., Szpak E., Andersson. M. and Bergelin, I.: Self-treatment using 0.25%-0.50% podophyllotoxin-ethanol solutions against penile condylomata acuminata: a placebo-controlled
30 comparative study. Genitourin. Med., 70: 105, 1994.

13. Syed, T.A. and Lundin, S.: Topical treatment of penile condylomata acuminata with podophyllotoxin 0.3% solution, 0.3% cream and 0.15% cream. A comparative open study. *Dermatology*, 187: 30, 1993.
14. Davis, B.E. and Noble, M.J.: Initial experience with combined interferon-alpha 2 B and carbon dioxide laser for the treatment of condylomata acuminata. *J. Urol.*, 147: 627, 1992.
15. Gross, G., Roussaki, A., Baur, S., Wiegand, M. and Mescheder, A.; Systemically administered interferon alfa-2a prevents recurrence of condylomata acuminata following CO2-laser ablation. The influence of the cyclic low-dose therapy regime. Results of a multicentre double-blind placebo-controlled clinical trial. *Genitourin. Med.*, 72:71, 1996
16. Monsonago, J., Cessot, G., Ince, S.E., Galazka, A.R and Abdul-Ahad, A.K.: Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin. Med.*, 72: 111, 1996.
17. Cardamakis, E., Kotoulas, I.-G., Metalinos, K, Mantouvalos, H., Relakis, K, Scapari, M. Korantzis, and Papathanasiou, Z.: Treatment of urethral condylomata acuminata or flat condylomata with interferon- α 2a. *J. Vol.* 152:2011, 1994.
18. Cardamakis, E.K. Kotoulas, I-G.B., Dimopoulos, D. P., Stathopoulos, E.N. Michopoulos, J.T. and Tzingounis, V.A: Comparative study of systemic interferon alfa-2a with oral isotretionin and oral isotretionin alone in the treatment of recurrent condylomata acuminata. *Arch. Gynecol. Obstet.*, 258: 35, 1996.

19. Tsambaos, D., Geogiou, S., Monastini, A., Sakkis, T., Sagriotis, A. and Georz G.: Treatment of condylomata acuminattta with oral isotretionin. J. Urol, 158: 1810, 1997
- 5
20. Monk, B.J. and Burger, R.A.: New Therapies for Genital Condyloma in Women, Contemp OB/Gyn. 1998; Feb.:81 to 96.
21. Baniel, J., Lev, Z., Engelstein, D. and Servadio, C.: Penile edema and meatal ulceration after intravesical instillation with bacillus Calmette-Guerin. Urology, 47: 932, 1996.
- 10
22. Sokal, R.R. and Rohlf, F.J.: Test of equality of 2 percentages In: Biometry W.H. Freeman Company, San Francisco, p.p. 607 to 608, 1969.
- 15

CLAIMS

1. A method of treatment of a disease condition caused by papilloma virus, which comprises:
5 applying an effective amount of a *Mycobacterium* to the region of infection.
2. The method of claim 1 wherein the papilloma virus is human papilloma virus.
10
3. The method of claim 2 wherein the disease condition include cutaneous and genital warts in humans.
4. The method of claim 2 wherein the disease condition is external
15 and intraurethral condylomata acuminata in humans.
5. The method of claim 1 wherein said *Mycobacterium* is an attenuated form of a *Mycobacterium* of the tuberculosis complex.
- 20 6. The method of claim 5 wherein said attenuated *Mycobacterium* is an attenuated form of *M. bovis*.
7. The method of claim 4 wherein said *Mycobacterium* is Bacillus Calmette-Guerin. (BCG).
25
8. The method of claim 1 wherein from about 1 to about 30 treatments of time interval from about 1 to about 30 days between treatments of more than one and the individual treatment dosage is from about 1 to about 500 mg of the *Mycobacterium*.
30
9. The method of claim 1 which is preceded by ablative surgery of the region of infection.

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10. The method of claim 9 wherein said ablative surgery is effected by laser.
- 5 11. The method of claim 1 wherein said *Mycobacterium* is formulated with a keratolytic agent for topical application to the region of infection.
- 10 12. The method of claim 11 wherein said *Mycobacterium* is formulated with said keratolytic agent as a cream for adherent application to the region of infection.
- 15 13. The method of claim 7 wherein said BCG is formulated with powdered salicylic acid as an adherent cream for application to the region of infection.
- 20 14. The method of claim 13 wherein said salicylic acid is present in an amount of about 0.1 to about 50 wt% of the composition.
- 25 15. The method of claim 14 wherein said salicylic acid is present in an amount of about 1 to about 10 wt%.
- 30 16. A therapeutic composition for the treatment of a disease condition caused by papilloma virus, comprising an effective amount of a *Mycobacterium* formulated with a keratolytic agent for topical application to a region of infection.
17. The composition of claim 16 wherein said *Mycobacterium* is an attenuated form of a *Mycobacterium* of the tuberculosis complex.
18. The composition of claim 17 wherein the *Mycobacterium* is an attenuated form of *M. bovis*.

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19. The composition of claim 16 wherein said *Mycobacterium* is Bacillus Calmette-Guerin (BCG).
20. The composition of claim 19 wherein said keratolytic agent is powdered salicylic acid.
21. The composition of claim 20 wherein said salicylic acid is present in an amount of from about 0.1 to about 50 wt% of the composition.
22. The composition of claim 21 wherein said salicylic acid is present in an amount of about 1 to about 10 wt%.
23. The composition of claim 16 which is formulated as a cream for adherent application to the region of infection.
24. The use of a *Mycobacterium* in the manufacture of a medicament for the treatment of infection caused by papilloma virus, particularly human papilloma virus.
25. The use of claim 24 including any application or preparation of the *Mycobacterium*, such as cream, powder, slow-release formulation, inhalation, enema or oral application.

Docket No.
10890-2 MIS

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

TREATMENT OF PAPILLOMA VIRUS INFECTION USING A MYCOBACTERIUM

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on April 29, 1999 as United States Application No. or PCT International Application Number PCT/EP99/02930 and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

April 29, 1998

(Filing Date)

(Filing Date)

(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

April 29, 1999

(Filing Date)

(Status)
(patented, pending, abandoned)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Michael I. Stewart (24,973) (1)

Send Correspondence to: Sim & McBurney
6th Floor, 330 University Avenue
Toronto, Ontario
Canada, M5G 1R7

Direct Telephone Calls to: *(name and telephone number)*
(416) 595-1155

Full name of sole or first inventor	<u>Andreas Böhle</u>	
Sole or first inventor's signature	<u>A. Böhle</u>	Date <u>4/12/2000</u>
Residence	<u>Gross Grönau, Germany</u> <u>DEX</u>	
Citizenship	<u>German</u>	
Post Office Address	<u>Fasanenring 2, D-23627 Gross Grönau, Germany.</u>	

Full name of second inventor, if any	<u>Dieter Jocham</u>	
Second inventor's signature	<u>Dieter Jocham</u>	Date <u>4/12/2000</u>
Residence	<u>Lübeck, Germany</u> <u>DEX</u>	
Citizenship	<u>German</u>	
Post Office Address	<u>Zwinglstrasse 1, D-23568 Lübeck, Germany.</u>	